Full Title: Neurodevelopment: The Impact of Nutrition and Inflammation During Early to Middle Childhood in Low Resource Settings

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Abbreviations: CNS – central nervous system; CSF – cerebrospinal fluid; CMV – cytomegalovirus; DNA - deoxyribonucleic acid; EEG – electroencephalography; ERP – event-related potential; fNIRS - Functional near-infrared spectroscopy; HIV – human immunodeficiency virus; LMIC – low- and middle-income countries; LRS – low resource settings; MRI - magnetic resonance imaging; MEG – magnetoencephalography; NDI - neurodevelopmental impairment; T4 – thyroxine; T3 – triiodothyronine; WASH - water, sanitation and hygiene

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- Dr. Chandy John was a panelist at the original NICHD scientific meeting, served as the lead author for the paper, organized the writing team, drafted the initial manuscript, incorporated edits from the additional authors and editors, finalized the manuscript, approved the final manuscript as submitted and is accountable for all aspects of the work.
- Dr. Maureen Black was a panelist at the original NICHD scientific meeting, contributed to the writing of the initial manuscript, reviewed and revised subsequent versions of the manuscript, approved the final manuscript as submitted and is accountable for all aspects of the work.

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Abstract:

The early to middle childhood years are a critical period for child neurodevelopment. Nutritional deficiencies, infection and inflammation are major contributors to impaired child neurodevelopment in these years, particularly in low resource settings. This review identifies global research priorities relating to nutrition, infection, and inflammation in early to middle childhood neurodevelopment. Research priority areas identified include: 1) assessment of how nutrition, infection or inflammation in the pre-conception, prenatal and infancy periods (or interventions in these periods) affect function in early to middle childhood; 2) assessment of whether effects of nutritional interventions vary by poverty or inflammation; 3) determination of the feasibility of pre-school and school-based integrated nutritional interventions; 4) improved assessment of the epidemiology of infection- and inflammation-related neurodevelopmental impairment (NDI); 5) identification of mechanisms through which infection causes NDI; 6) identification of non-infectious causes of inflammation-related NDI and interventions for causes already identified (e.g, environmental factors); and 7) studies on the effects of interactions between nutritional, infectious and inflammatory factors on neurodevelopment in early to middle childhood. Areas of emerging importance which require further study include the effects of maternal Zika virus infection, childhood environmental enteropathy, and alterations in the child's microbiome on neurodevelopment in early to middle childhood. Research in these key areas will be critical to the development of interventions to optimize the neurodevelopmental potential of children worldwide in the early to middle childhood years.

Introduction

The foundations of health and well-being stem from the interplay between genes and environment that begin as early as conception and extend through early and middle childhood (ages 3-12 years).[1, 2] Children with adequate opportunities for early care and learning, nutrition, and protection from infectious and non-infectious causes of inflammation have the best chances of thriving. In contrast, children raised in adverse conditions, characterized by poverty, limited access to opportunities for early learning and responsive caregiving, nutritional deprivation, and infectious and non-infectious threats are at risk for negative health and social outcomes throughout their life-course, beginning with neurodevelopmental delays and extending to poor academic functioning, chronic diseases, mental illness, and lack of economic productivity.[2]

Global estimates are that over one-third of children under 5 years of age in low- and middle-income countries (LMIC) are at risk of not reaching their developmental potential, based on poverty and stunting.[3] However, without consideration of infectious and non-infectious causes of inflammation or nutritional deficiencies that do not result in stunting, the problem is likely to be much larger. Children who lag behind developmental expectations prior to age 5 are at risk for subsequent academic and socio-emotional problems as they approach middle childhood and primary school. Primary school prepares children for higher education and for the economic, interpersonal, social, and civic responsibilities of adulthood. Universal primary education is a central global goal, as illustrated by its inclusion in the Millennium Development Goals (Goal #2) and in the current Sustainable Development Goals (Goal #4).

Primary school enrollment has increased dramatically over the past two decades, especially in LMICs.[4] Based on World Bank data, for the lowest income countries, the primary school gross enrollment rate (i.e., number of children enrolled as a percentage of the eligible

population) for both boys and girls increased from 21% in 1996-2000 to 67% in 2011-2015.[5] However, access and retention continue to be concerns, and the 2015 Global Monitoring Report indicates that 58 million primary school-age children were out of school in 2015.[4] In addition to low enrollment and attendance related to crisis and conflict, distance, and denial of access, problems related to children's health and nutrition interfere not only with children's participation in primary school, but also their ability to learn.

Key Neurodevelopmental Considerations During Early to Middle Childhood

Although the groundwork for brain development begins just a few weeks after conception and continues through the first postnatal years of life, experience during middle and late childhood can still exert a tremendous influence on changes in synapse number and myelin integrity, as both processes continue to develop well beyond the first years of life.[6] It is during this time that nutrition and inflammation, for example, can have a large impact on myelination, and that exposure to multiple forms of adversity can impact the development of learning and memory circuits that reside in the medial temporal lobe (e.g., hippocampus), and the development of executive functions (subserved by a distributed network of regions in the prefrontal cortex). Importantly, the biggest shift in both gray and white matter occurs as children make the transition to puberty.[7] During this time, gray matter declines first followed by white matter, a process that starts right before puberty and may continue for another decade. This process is advanced in girls as compared to boys by one to two years; consequently, girls enter these events earlier and conclude sooner than do boys.[8,9] Thus, even if children traverse the infancy period – a critical time for many aspects of brain development – various environmental factors can still impact brain development during later periods (See Figure 1).

Furthermore, our understanding of the developmental sequence, as well as the genetic

and experiential contributions to brain development, have grown tremendously over the past few decades. So, too, has our knowledge of more functional aspects of brain development in the first 2+ years of life, largely due to advances in imaging tools suitable for young infants such as electroencephalography (EEG), event-related potential (ERP), and functional near-infrared spectroscopy (fNIRS).[10,11] However, there are enormous gaps in our knowledge of structural and functional brain development during the early and middle childhood periods, for several reasons.

First, with the exception of the increasingly rare primate models of development, rodent models do a relatively poor job of simulating human brain development during the preschool and elementary school years. Second, the use of EEG and ERP methods (fNIRS is still a relatively recent addition to our imaging armamentarium) remains stubbornly difficult in younger children, mostly due to their inherent resistance to sitting still for long periods of time coupled with motor limitations that make overt responding difficult. Similarly, structural and functional magnetic resonance imaging (MRI) and to a limited extent, magnetoencephalography (MEG), has led to important new discoveries about brain development during middle childhood, while these tools are enormously difficult to use in children under 5 years of age. Finally, significant attention has been paid to malnutrition early in life, with far less attention paid to inflammatory disease and the effects these two forms of adversity exert on older children, particularly those with an early developmental history of malnutrition or illness.

The Impact of Nutrition on Neurodevelopment During Early to Middle Childhood

Food insecurity, or inconsistent access and availability to a diverse, safe and nutritionally adequate diet for an active life style, a primary cause of nutritional deprivation, is associated with poverty and may impact both the quantity and quality of available food, contributing to lack of macro- and micronutrients. Macronutrients include energy, carbohydrates, and fat, while

micronutrients include small quantities of vitamins and minerals, such as iron, zinc, and vitamin B12, required for specific physiological functions. At least four micronutrients have been associated with neurodevelopment during early to middle childhood: iodine, zinc, vitamin B12, and iron.

School-age children in food insecure households are at risk for academic and behavioral problems, which may be related to a lack of nutrients and to stress associated with an inconsistent food supply. Neuroscientific evidence has documented the adverse and pervasive role of poverty on early brain development, specifically on psychoimmunological functioning and self-regulation,[12] but there has been little attention to the combined effects of poverty and nutritional deficiencies on neurodevelopment.

Childhood stunting, closely associated with poverty and a major threat to child development, is often used as a population-based indicator to compare nutritional adequacy across countries. A recent meta-analysis on the association between linear growth and children's development included 68 reports from 29 LMICs[13] and found that early growth restriction is associated with lower cognitive scores throughout childhood. Findings related to socioemotional development were less clear, primarily due to the small number of studies and differences in measurement of socioemotional development across differing ages.

At least three mechanisms may link early stunting to development during early to middle childhood: 1) biological insults that disrupt early brain development, 2) delayed motor skills that may disrupt the exploration associated with cognitive development, and 3) reduced expectations from parents and peers, based on short stature. The long-term consequences of stunting extend beyond childhood into adulthood and include lower height, less schooling and reduced economic productivity.[14,15] Studies into the next generation have shown associations between first

generation stunting and offspring birth size[15] and performance on cognitive assessments.[16]

Although most of the research linking nutrition with inflammation and neurodevelopment focuses on undernutrition, overnutrition such as childhood obesity has also become a global concern. Obesity begins early in life, increases during childhood and adolescence, and has been associated with impaired cognition. Possible mechanisms include altered brain structure, leptin/insulin regulation, oxidative stress, cerebrovascular function, blood-brain barrier, inflammation, and decreased motor performance associated with a degraded musculoskeletal system.[17]

Micronutrients

Iodine

Iodine deficiency disrupts production of thyroid hormones, thyroxine (T4) and triiodothyronine (T3), which are necessary for neurogenesis, neuronal migration, synaptogenesis, and myelination.[18,19] Severe deficiency can cause goiter and intellectual disability and even mild/moderate deficiencies are associated with intellectual delays that can disrupt academic functioning.[18] Iodine supplementation trials appear to partially reduce the negative effects of iodine deficiency, but ensuring adequate maternal iodine status prenatally can prevent iodine deficiency during the period of rapid brain development.[18]

Zinc

Zinc plays a critical role in central nervous system (CNS) development, specifically neuron formation, migration, and synapse generation.[20] Zinc is found in high concentrations in the hippocampus, cerebellum, pre-frontal cortex, cortex, and limbic system; and animal studies have documented zinc's role in neurodevelopment.[19, 21] Evidence from human supplementation trials has found positive associations between prenatal or infant zinc supplementation and motor

development, including processing speed and motor aspects of attention, but not with measures of cognitive processing.[21] One supplementation trial conducted among school-age children in China found beneficial effects of zinc supplementation on neuropsychological functioning when zinc was combined with other micronutrients, [22] but trials of zinc supplementation alone among school-age children conducted in Canada and Guatemala found no effects on cognition or academic performance. [23]

Vitamin B12

Vitamin B12 plays an important role in multiple fetal developmental processes, including neurodevelopment through DNA methylation and epinephrine synthesis, along with methionine synthesis.[24] The fetus receives vitamin B12 through the placenta from maternal vitamin B12.[25] After birth, vitamin B12 deficiency is supplied through animal source food. Vitamin B12 deficiency has been associated with demyelination, which can result in delayed cognitive development, and with gastric inflammatory states, possibly indicating an inflammation induced autoimmune process blocking intrinsic factor and thus preventing vitamin B12 absorption.[26]

Although longitudinal studies have shown a relation between prenatal vitamin B12 deficiency and school-age cognitive functioning involving the frontal lobe (perceptual tracking and simple sequencing tasks) and temporal lobe (short term memory),[27] more research is needed to understand vitamin B12's role in neurodevelopment, and links to academic performance.

Iron

Iron deficiency is the most common nutrient deficiency globally; through its role in hemoglobin synthesis, adequate iron is essential for oxygen delivery to all tissues, especially the brain. Iron is necessary for myelination, frontal cortex, and basal ganglia development.[28] In toddlerhood, iron deficiency has been associated with impaired social-emotional behavior,

including shyness, wariness, and low responsivity.[29] Iron deficiency anemia in early infancy is a risk factor for impaired mental and motor development and has been associated with long-term negative functional consequences.[19]

Although the associations between iron deficiency and infant and child development are strong, nutritional interventions early in life, when children's rate of growth is rapid and nutritional demands are high, have met with limited and inconsistent success either in alleviating nutritional deficiencies or in promoting early development.[30, 31] Possible explanations for the limited findings are: 1) the origins of iron deficiency may occur prior to conception or prenatally, and postnatal interventions are too late; 2) interventions may be most effective when targeted to deficient populations; or 3) iron deficiency often occurs in the context of other micronutrient deficiencies, leading to recommendations to focus on multiple micronutrient deficiencies.[32]

Multiple Micronutrients

Micronutrient deficiencies often co-occur, especially when micronutrients are derived from common sources, such as animal source foods. Recent evidence suggests that interventions supplementing multiple micronutrients are more beneficial than single micronutrient trials for child development.[19] Reviews of multiple micronutrient supplementation trials administered prenatally through school-age on neurodevelopmental performance have yielded mixed findings. Although at least one has found an impact of prenatal iron-folic acid supplementation on school-age neurodevelopmental performance, [33] others have reported reductions in anemia, with no changes in neurodevelopmental performance. However, few intervention trials have followed children into school-age. Two reviews of multiple micronutrient supplementation[34] or fortification[35] introduced during school-age have reported inconsistent findings related to cognition and academic performance.

In addition to adequate nutrition, neurodevelopment is dependent on environmental opportunities for responsive caregiving and early learning. Integrated interventions that combine nutrients with opportunities for responsive caregiving and early learning have been recommended,[36] and evidence suggests that trials that include both early education and nutrition are more likely to result in cognitive benefits than single intervention trials,[37,38] but relatively few integrated trials or programs have been evaluated systematically.[39] Table 1 provides a summary of key gaps in knowledge related to nutrition and neurodevelopment in early to middle child development.

The Impact of Inflammation on Neurodevelopment During Early to Middle Childhood

Fetal exposure to maternal infection and inflammation may have long-term consequences well into early to middle childhood, though these effects are more often studied during the infancy and adolescent periods. This may be because the critical period of brain development from 0-3 years and the interactive effects of hormonal changes in adolescence focus attention on these age groups. Yet, the available evidence suggests a potential for a profound effect of maternal infection on neurodevelopment in early to middle childhood.

Symptomatic congenital cytomegalovirus (CMV) infection is among the best described congenital infections associated with cognitive impairment in children, starting in infancy and affecting children of all ages.[40] In contrast, asymptomatic CMV infection is far more common than symptomatic infection, but is associated with cognitive impairment only in school age[41,42] and not older [41] children. Limited data from children exposed in utero to maternal HIV infection and antiretroviral drugs but uninfected with HIV themselves,[43,44] and from experimental models of malaria exposure in utero,[45] suggest that children in early to middle childhood are affected by maternal infection or inflammation. Numerous studies document the effects of vertically

acquired HIV infection in multiple areas of neurodevelopment in school age children including overall cognitive ability,[46,47] memory, perception,[48] motor function,[49, 50] executive function,[51] and language skills.[50, 52] Maternal helminth infection shows effects on children at 1 year of age that may well extend into early to middle childhood,[53] but these effects are so far unstudied. Findings like this highlight the need for longitudinal studies of the effects of maternal or congenital infections on child neurodevelopment across the age span. The most striking recent example of congenital infection affecting the CNS is Zika virus infection,[54] and the full effects of this newly emerging infection on child neurodevelopment remain to be described.[55]

Many infections that occur in children can occur across ages, from the neonatal period to infancy and early to middle childhood. The most common of these infections worldwide, such as helminth infection, diarrheal disease, and malaria, are typically most frequent in children under 3 years of age, but the effects of infection in the younger years often lasts into early or middle childhood, and infection does continue, albeit with less frequency and severity, through the latter period.

Diarrheal disease in the first two years of life has also been associated with cognitive impairment in early to middle childhood in a number of studies, notably from Brazil[56-58] and Bangladesh.[59] Other infections with well-documented effects on neurodevelopment in school age children include intestinal helminths,[60-63] schistosomiasis,[60, 64] and malaria.[65-69] Other than HIV, none of these infections directly infect the CNS; they all act through indirect mechanisms that are still poorly described, yet likely involve inflammation. Because of their high incidence, these infections likely affect neurodevelopment in many more children than infections that directly infect the CNS, such as HIV, bacterial meningitis and viral encephalitis.

The studies cited above are examples of the substantial body of data showing the effects

of infection and inflammation, at various stages, on neurodevelopment during early to middle childhood. However, a recent review noted that for most infections that affect the CNS, reliable estimates of the incidence of resulting neurodevelopmental impairment are not currently available.[70] Without this information, it is difficult to determine the burden of infection-related neurodevelopmental impairment in early to middle childhood or implement appropriate interventions. To obtain accurate estimates, better diagnostics (ideally low-cost and point-of-care), more in-depth surveillance and epidemiologic studies are required.

Further, studies of the pathogenesis of how infection leads to neurodevelopmental impairment are urgently needed, as these mechanisms remain largely unknown or poorly characterized, and are not limited solely to inflammation. Infection may lead to neurodevelopmental impairment through direct CNS injury by the infectious pathogen or, for example, through pathways such as sequestration and endothelial activation in cerebral malaria[71] that may involve inflammation as one component but may not be traditionally defined as inflammation. Thus, an understanding of pathogen mechanisms of direct injury and the full range of the host response, including pathways not related to inflammation or of which inflammation is only a component, is another important area for future research. Such research will require better markers of inflammation, tissue injury and host response, including non-invasive surrogate markers of CNS infection, inflammation and injury. Current systemic assessments have clear limitations, as they may not reflect CNS findings, and, indeed, in studies in which CNS markers have been assessed through cerebrospinal fluid (CSF) or brain biopsy, systemic findings often differ from CNS findings.

Inflammation may also affect child neurodevelopment through non-infectious causes. There is an emerging literature on environmental causes that have been associated with impaired

child neurodevelopment, including maternal or child tobacco, pollutant and pesticide exposure.[72-75] A few studies have documented an association of environmental pollutants with systemic inflammation[72,73] and impaired neurodevelopment, suggesting that inflammation could be a mechanism by which these factors affect neurodevelopment. However, there are no studies to date that actually define the pathways by which environmental exposures cause impaired neurodevelopment, highlighting another key area for future research. Table 2 summarizes key gaps in knowledge related to inflammation and neurodevelopment during early to middle childhood.

The Interaction of Nutrition, Inflammation, Neurodevelopment, and Other Influencing Factors During Early to Middle Childhood

Interactions between nutrition, infection, inflammation and environmental factors are clearly important in neurodevelopmental impairment in early to middle childhood. Micronutrient deficiency, infection and inflammation interact in complex ways. That is, micronutrient deficiency may predispose to or protect from infection, and may predispose to increased or decreased inflammation, but conversely, inflammation and infection may lead to micronutrient deficiency. For example, iron deficiency appears to provide fairly strong protection against clinical malaria,[76] yet malaria-associated inflammation and upregulation of hepcidin likely leads to decreased iron bioavailability and functional iron deficiency. Both malaria and iron deficiency can lead to neurodevelopmental and behavioral impairment, and children in malaria endemic areas may also have inflammation due to other causes, e.g., helminth infection, that can also lead to neurodevelopmental impairment. With these complicated relationships, untangling how each factor relates to the other and how each contributes to neurodevelopmental impairment can be difficult, but is critical if interventions in endemic areas are to successfully prevent neurodevelopmental impairment without increasing risk of infection.

Anemia of inflammation, often due to infectious causes, is another understudied but likely frequent cause of neurodevelopmental impairment in children in LRS. A study in the Philippines showed that children with anemia of inflammation, who did not have iron deficiency by standard biomarkers, had lower cognitive scores than those without anemia. The authors hypothesized that the worsened outcomes were due to decreased delivery of iron to end organs, including the brain.[77] This study illustrates complex interactions and the importance of understanding mechanisms of disease, since the children with anemia of inflammation were not iron deficient by standard biomarker measurements, but were likely functionally iron deficient in key end organs, including the brain. Research that contributes to a better definition of the infection and inflammation-associated pathways that lead to neurodevelopmental impairment, and how these pathways affect micronutrients, provides the best opportunity to determine the various contributions of these factors to neurodevelopmental impairment. In addition, such research is needed to help plan for interventions that improve neurodevelopment without disturbing the delicate homeostasis of these relationships in such a way that risk of infection, inflammation or micronutrient deficiency is increased.

Two emerging areas of interest that highlight interactive effects throughout childhood are the microbiome and environmental enteropathy. Inflammation and malnutrition can alter the microbiome, and, conversely, changes in the microbiome can affect both nutrition and systemic inflammation.[78] Changes in the microbiome have been hypothesized to potentially influence changes in child neurodevelopment and behavior through the "microbiome-gut-brain axis."[79] Similarly, environmental enteropathy, involving intestinal inflammation without overt diarrhea, also seems to affect risk of both malnutrition and impaired child neurodevelopment.[80] Alterations in the microbiome are very likely to occur in environmental enteropathy, and indeed

might be part of the pathogenesis of this process. Future research studies should assess how both factors may affect child neurodevelopment in early to middle childhood, how each condition affects the other, and interactions with inflammation, malnutrition and micronutrient deficiency. Water, sanitation and hygiene (WASH) programs may have a role in decreasing environmental enteropathy and have been proposed as a component of early childhood development programs. [81] Given the complex interactions of microbes, nutritional factors and inflammation, the components of these programs will need careful consideration and study for optimal effectiveness.

Finally, children with disabilities and neurodevelopmental and neurocognitive issues experience numerous challenges in early to middle childhood. Their access to educational opportunities is often limited, nutritional problems may occur if they have swallowing, motor or cognitive problems that affect their ability or desire to eat nutritious foods, and they may be neglected in favor of children without impairment. These problems may become particularly acute in settings where resources are limited. These challenges can make children with neurodevelopmental impairment more susceptible to nutritional deficiencies and infectious/inflammatory exposures than children without neurodevelopmental impairment. Thus, while the primary focus of this paper has been on the effects of infection, inflammation, and nutrition on neurodevelopment, neurodevelopment may also tie back and affect these factors. Table 3 summarizes current gaps in knowledge related to interactions between nutrition, inflammation, neurodevelopment, and other influencing factors during early to middle childhood.

Implications for Research, Program, and Policy Development

Primary prevention of infectious and non-infectious inflammation and nutritional deficiencies beginning prior to conception and extending through childhood would protect children from these threats to early brain development. Children who have avoided early threats or who have emerged with relatively few negative consequences have often been protected by responsive caregiving.[82] In a striking example, at age 12, children raised in Romanian orphanages and randomized at 18-24 months to high-quality foster care showed stress responses (marked by cortisol and parasympathetic nervous system reactivity) that differed from children randomized to remain in the orphanages and approached responses expected of non-institutionalized children.[83] The foster care group also continued to show better brain electrical activity, measured by EEG, as long as they remained in high-quality foster care.[11] This neuroscientific evidence provides support for early intervention programs that focus on responsive caregiving.

Furthermore, preprimary educational programs that include well-qualified personnel working with both parents and children can have beneficial effects on children's cognitive performance [84] and prepare children for primary school.[85] Recent evidence has illustrated the beneficial effects of incorporating neurodevelopmentally-based teaching methods into preprimary classes, particularly among children from low-income families.[86] Skills often categorized as self-regulation (e.g., the ability to attend, to regulate emotions and behavior, and to participate in goal-directed activities) are positively related not only to school-age learning and academic performance, but also to adult well-being.[87,88] Self-regulation is influenced both by underlying neural and physiological systems and by environmental expectations, suggesting that it is potentially responsive to interventions. In a trial in which self-regulation activities were systematically incorporated into kindergarten classes (e.g., cooperative activities that promote

socio-emotional and cognitive development, reflective "talk," make-believe play), children experienced improvements in measures of self-regulation, in neuroendocrine functioning, and in academic measures of reading and mathematics.[89] The academic benefits were retained through first grade, suggesting that exposure to self-regulation-promoting activities during the middle childhood years may promote subsequent neurodevelopment by enhancing self-regulation and possibly mitigate some of the negative effects of early nutritional deficiencies and inflammation. School feeding programs have been implemented in many resource-limited settings to reduce hunger, promote attendance, and enhance academic performance. A recent review found that school feeding programs have a positive impact on energy intake, micronutrient status, school enrollment, and attendance, with inconsistent effects on growth, cognition, and academic achievement. [90] The authors postulate these mixed findings may be attributable to a multitude of factors including differences in the objectives and methodologies used, quality and quantity of food served, duration of the interventions, degree of malnourishment, and severity of comorbid conditions such as helminth infection. These findings demonstrate the complexity of assessing neurodevelopmental outcomes in the context of multiple co-occurring and variable risk factors across the life course.

Most studies of neurodevelopmental impairment are association studies that cannot prove causation. There are multiple reasons why there are few longitudinal studies of children, a key barrier being the high cost of following the very large cohorts required. For example, disease states such as cerebral malaria are not common in any given cohort, even though, across malaria endemic areas, hundreds of thousands of children are affected annually. However, for nutritional, infectious/inflammatory, or environmental factors that occur with sufficient frequency, birth cohort studies provide an opportunity to better define the causes of neurodevelopmental

impairment, and interactions between factors leading to this impairment, than can be achieved with cross-sectional studies. For example, despite multiple studies showing an association between uncomplicated or severe malaria and cognitive impairment, a large cluster randomized study of intermittent screening and treatment for malaria in school age children showed that this intervention did not improve educational achievement and was associated with a negative effect in spelling and arithmetic scores.[91] This study suggests that earlier intervention may be required, or that malaria may be a proxy for other causes of neurodevelopmental impairment. The failure of randomized controlled trials to detect a treatment effect highlights the need for further research on the mechanisms of neurodevelopmental impairment and the importance of interventions for optimal neurodevelopment in early and middle childhood.

Responsive caregiving and early learning may mitigate some of the neuropsychological effects of adversity, emphasizing the importance of interventions to children's health and well-being. In spite of the positive evaluations on the impact of early learning and responsive caregiving interventions,[37, 38, 92, 93] few intervention options are available for children and families. Future recommendations include strategies to integrate, monitor, and sustain effective interventions for young children.

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Table 1. Gaps in Knowledge Related to Nutrition and Neurodevelopment During Early to Middle Childhood

Problem or Question	Studies Needed
What is the impact of early nutritional deficiencies on neurodevelopment and brain function during early to middle childhood?	1) Identify sensitive periods in terms of timing of intervention. 2) Determine how much plasticity there is in recovery from early nutritional deficiencies and whether interventions can be developed for implementation after a sensitive period has closed.

Individual differences in timing of nutritional intervention and recovery from early deprivation.	Identify genes that may play a role in individual differences; develop new intervention strategies.
Are there lasting effects of nutritional interventions implemented during the pre-conception, prenatal, infancy, and preschool periods on functioning during early to middle childhood?	1) Longitudinal follow-up through middle childhood of interventions delivered at earlier time periods. 2) Measure nutritional status, brain structure and function, and academic performance.
Do the effects of early nutritional interventions vary by poverty or inflammation?	Examine how poverty and inflammation modify the above relationships.
Are preschool/school-based integrated interventions that include nutrition and early child development (e.g., self-regulation) feasible and effective?	Conduct a trial of integrated interventions in preschool/school settings and measure impact on nutritional status, executive function, and academic performance.
Can school feeding programs be implemented that are effective in promoting school performance while not increasing stigma?	Evaluate strategies to introduce school feeding programs that are effective and examine perceptions of stigma.

Table 2. Gaps in Knowledge Related to Inflammation and Neurodevelopment During Early to Middle Childhood	
Problem or Question	**Studies Needed**
What is the burden of neurodevelopmental impairment (NDI) from specific infections or inflammation in children in early to middle childhood?	1) Low-cost, point-of-care, easy to use, accurate diagnostics for infection and inflammation. 2) Define the epidemiology of infection- and inflammation-related NDI.
How does infection or inflammation during pregnancy or in early infancy affect a child's neurodevelopment in early to middle childhood and beyond?	1) Longitudinal studies (including birth cohort studies) of infection and inflammation-related NDI that follow children up through early to middle childhood and beyond. 2) Define correspondence validity of tests that measure specific areas of neurodevelopment in age groups that span infancy to adolescence.
How does infection cause NDI? What are the roles of direct injury, inflammation, or other pathways in infection-related NDI?	1) Define pathogenesis of infection-related NDI. 2) Determine the contributions of direct pathogen injury, infection-related inflammation, and other infection-related pathways (e.g., endothelial activation) to NDI. 3) Define non-invasive surrogate markers of brain infection, inflammation and injury. 4) Assess interaction of these pathways in causing NDI.
What are the non-infectious causes of inflammation in early to middle childhood?	1) Assess inflammation longitudinally in children. 2) Determine environmental and other causes of inflammation in early to middle childhood.
How do environmental factors lead to impaired NDI?	1) Define how environmental factors (e.g., pollutants, tobacco use, toxins) relate to NDI. 2) Assess environmental contributions to inflammation-related and non-inflammation-related NDI. 3) Define the specific areas of the brain/ cognition/behavior affected by particular environmental factors.
Can prevention of environmental, infectious or inflammatory factors decrease NDI?	1) Well designed clinical trials to assess whether interventions that reduce known environmental, infectious or inflammatory risk factors for NDI can reduce NDI in

	early to middle childhood. 2) Inclusion of NDI as an endpoint in studies aiming to reduce infection, environmental pollution or toxins.
Can adjunctive treatments decrease infection-related NDI?	Well-designed clinical trials of interventions that appear to block infection-related pathways leading to NDI.

Table 3. Gaps in Knowledge Related to Interactions of Nutrition, Inflammation, Neurodevelopment, and Other Influencing Factors During Early to Middle Childhood	
Problem or Question	**Studies Needed**
How do interactions of micronutrient deficiency, infection and inflammation in a pregnant woman affect neurodevelopment in her child in early to middle childhood?	1) Assess micronutrient deficiency, infection and inflammation in pregnant women at all stages of pregnancy. 2) Determine the effects of individual factors and interactions between these factors on fetal growth, placental pathology, and long-term neurodevelopment in the affected child in early to middle childhood. 3) Example of a specific study: how do malaria and helminth infection affect development of iron deficiency; what is the role of inflammation in this interaction; how does iron deficiency affect risk of malaria and helminth infection; and how do the four factors together affect risk of NDI in endemic areas?
Why and how does environmental enteropathy develop?	Determine the factors and mechanisms that lead to environmental enteropathy.
How does environmental enteropathy contribute to NDI?	Define the pathways by which environmental enteropathy leads to NDI.
How do changes in the microbiome relate to environmental enteropathy and vice versa?	Determine the effects of changes in the microbiome on environmental enteropathy, and of development of environmental enteropathy on the microbiome.
What are the interactions between micronutrient deficiency, the microbiome and malnutrition, and how do these related to NDI?	Comprehensively assess how micronutrient deficiency, the microbiome and malnutrition interact during pregnancy in the mother, and during infancy and early to middle childhood in the child, lead to early to middle childhood NDI.
How do interactions between micronutrient deficiency, infection and inflammation in early to middle childhood affect neurodevelopment?	1) Determine how micronutrient deficiency, infection and inflammation interact from infancy through early to middle childhood. 2) Assess how interactions between these three factors in infancy or early to middle childhood contribute to NDI.
How does impaired neurodevelopment affect risk of infection, inflammation and environmental toxins or pollutants?	Study the risks of infection and infectious or inflammatory processes, and the risk of environmental toxin or pollutant exposure in children across the spectrum of neurodevelopment.
What is the relation between structural and functional brain development during middle childhood?	1) Better methods to measure both structural and functional brain development among preschool and early school-age children.

	2) Examine the impact of nutrition and inflammation on brain structure and function during middle childhood and the concordance between brain structure and function.

Figure 1: Relationships among individual and environmental risk factors, inflammation, nutrition and neurodevelopment for school-age children in low resource settings.